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Feature Article

Oscillatory chemical reactions in the quest for rhythmic motion of smart materials

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ABSTRACT

Oscillatory chemical reactions have been drawing the attention of researchers for a number of decades. More recently, the ability of the reactions to work as the driving force for smart materials became attractive in the quest for biomedical applications, such as pulsatile drug delivery and controlled tissue proliferation. Owing to recent developments in the field, these fascinating reactions have advanced from taking place in solution to polymer based soft materials. In this review we discuss the current state of the art and steps on the way to fully autonomous all-polymeric rhythmic materials and share our personal perspective about the future of oscillatory chemical reactions.

1. Introduction

While oscillatory chemical processes as natural phenomena are millions of years old, their systematic studies have more recent origins and what can only be described as a very bumpy journey to scientific recognition. The first published records of oscillations in chemical systems date from 1828, when Fechner described oscillating current produced by an electrochemical cell [1], however the research area was not firmly established until the mid-1970s. It took numerous recordings of oscillatory behavior, mathematical modelling and discussions of the observed phenomena throughout the 19th and 20th centuries before the academic community was convinced that oscillatory chemical reactions are genuinely feasible chemical processes, where the concentration of a species increases and decreases ('oscillates') periodically over time [2–4]. A barrier to accepting this phenomenon was that this has been wrongly seen as an analogue to a *physical pendulum*, transiting equilibrium multiple times and therefore contradicting the Second Law of Thermodynamics ($\Delta S_{total} \geq 0$, where ΔS_{total} is the total entropy change of an isolated system). On the contrary, Prigogine (who was awarded a Nobel Prize in chemistry for these studies) and colleagues showed that in oscillatory chemical systems, each oscillation ***never passes through the equilibrium point***, but rather operates far from equilibrium, on the way towards equilibrium, strictly abiding by the laws of non-equilibrium thermodynamics [5,6]. Thus, in a chemical system, the concentration of intermediates and catalytic species can oscillate over time while the free energy monotonically decreases as a result of the continuing conversion of high free energy reactants into low free energy products. In this way, any decrease in entropy due to the periodic concentration changes is more than compensated for by an entropy increase from other processes [7–9]. This understanding led to what we now know as the area of Nonlinear Chemical Dynamics (NCD). In the past five decades, NCD has grown enormously and found application in multiple areas of science, describing various key phenomena not explained by conventional dynamics methods: from biology (studies of animal coat patterns, such as those in leopards, zebras, cheetahs; quorum sensing in bacteria; human electrophysiology; living cell cycle), smart materials ('chemical computer'), geology (hexagonal rock formations) to ecology and sociology [10–18]. For example, a number of oscillatory reactions are able to produce spatiotemporal wave patterns, creating stable colour variations similar to those in

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zebra or leopard coats [7]. These patterns are often referred to as Turing patterns, owing to Alan Turing's ground-breaking reaction-diffusion theory [19]. Turing was the first to suggest that the breaking of symmetry in biological systems was due to the difference in reaction and diffusion rates of two main components, where one is autocatalytic and the other is an inhibitor for the first component. This idea has since been applied to describe feather colour patterns in birds and skin colour in animals by identifying appropriate 'autocatalytic' and 'inhibiting' genes and proteins [20–22]. Under laboratory conditions in a well-mixed solution, the changes caused by autocatalytic and inhibiting components are typically manifested as periodic oscillations in colour, pH, redox potential and component concentration [23–33].

As a bridge between natural phenomena and artificial designs, oscillatory chemical reactions form a solid basis for further exploration of NCD and the opportunities it provides for materials research. Developments in laboratory oscillatory reactions have allowed them to be exploited as driving mechanisms for molecular motors and machines, where the chemical energy is efficiently converted into mechanical energy [34–36]. While oscillating, the change in the oxidation state of a certain species and/or release of energy of the reaction periodically engages with the 'mechanical' part that by a response enacts the machine. The response of the machine is potentially tunable to its intended application: motion for propagating chemical waves or artificial cilia, change of colour for sensor applications, volume or electrical properties. The most promising 'mechanical' parts are so-called 'smart' or 'responsive' materials. Smart materials significantly and reversibly alter their properties (e.g. shape, size, volume or colour) in response to external stimuli, such as humidity, stress, electric or magnetic field or pH and thus are extremely important for a wide range of applications, from biomimetics to nanoelectronics [37–41]. In this review, we discuss the current state-of-the-art in oscillatory reactions as a driving force for smart materials, the future of the area and present our personal perspective.

2. From small molecule to polymer systems

The cornerstone oscillatory chemical reaction for application in smart materials research is the **Belousov–Zhabotinsky (BZ) reaction** [8,42]**,** which involves oxidation of an organic substrate, e.g. malonic or citric acid, by bromate ion in the presence of a strong acid and a metal catalyst (cerium ion, ferroin or lately, tris(bipyridine)ruthenium(II) chloride). During the reaction, the catalyst undergoes spontaneous redox oscillations, and bromate is autocatalytically reduced to bromine and subsequently recovered. For any oscillatory reaction, autocatalysis is the key part in the complex reaction mechanism, and is the subject of numerous scientific studies. The commonly agreed mechanism of the BZ reaction follows a model proposed by Field, Körös and Noyes, consisting of three main cyclic subprocesses: (i) consumption of bromide ion by bromate; (ii) autocatalytic consumption of generated bromous acid accompanied by catalyst oxidation and (iii) reduction of catalyst and substrate conversion [43]. Although the whole mechanism of the reaction is more complex and involves more steps and intermediates, this model allows numerical simulation of different aspects of the reaction.

The deep understanding of the BZ reaction has led to the development of more complicated oscillatory systems in which oscillations in solution are coupled with responsive polymers to form so-called 'self-oscillating' polymer gels, pioneered by Prof Yoshida's group from Tokyo University [44]. Their ground-breaking proof-of-concept material (Fig. 1) was essentially a copolymer of a pH-responsive block (pNIPAAm) and a ruthenium catalyst block, produced by atom-transfer radical polymerisation (ATRP) [45]. The hydrophilicity of the oxidised catalyst ($Ru(bpy)_3^{3+}$) was higher than that of the reduced catalyst ($Ru(bpy)_3^{2+}$) which resulted in changes in the swelling ratio of the gel, depending on the redox potential. Being rigid, the catalyst block served as a mechanical crosslinker for the hydrogel. The redox oscillations occurring in the core of the polymer system (the catalyst block) caused periodic swelling and collapsing of the gel, as observed from transmittance studies. Tuning the composition of the polymer by adjusting the

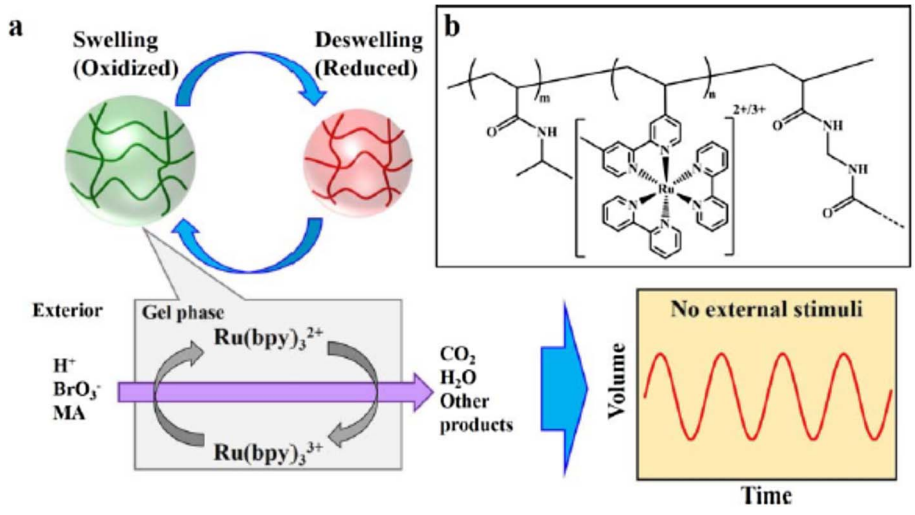

Fig. 1. (a) Design concept of the self-oscillating gel. (b) The chemical structure of p(NIPAAm-r-$Ru(bpy)_3$) gels. Reproduced with permission of John Wiley and Sons from Ref. [47].

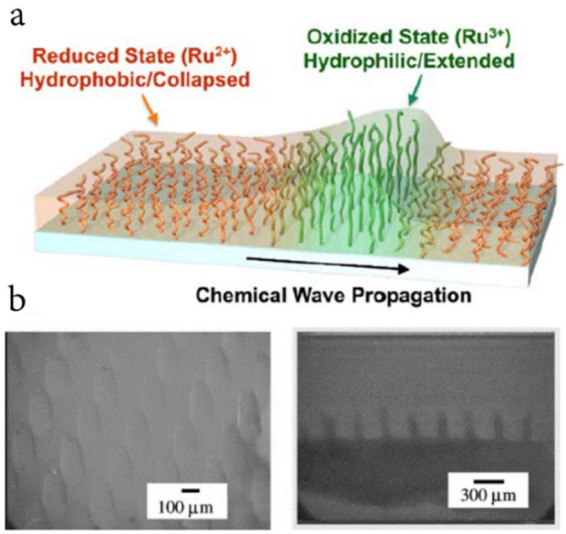

Fig. 2. (a) Schematic of the self-oscillating polymer brushes made by Yoshida. Reproduced with permission of John Wiley and Sons from Ref. [47]. (b) Top view (left) and side view (right) of the cilia-shaped self-oscillating gel fabricated by X-ray lithography and micromolding technique with bottom diameter of 100 µm and height of 300 µm. Reproduced from Ref. [36] with permission from Elsevier.

content of pNIPAAm allowed oscillations at 37 °C to be achieved [46]. After a number of modifications, the material was successfully fabricated by Yoshida and coworkers into a vast number of self-oscillating systems, including polymer brushes, tubular gels for mass transport systems, micelles and vesicles [47].

For example, they demonstrated that self-oscillating polymer brushes operate like artificial cilia (Fig. 2a), capable of sensing the chemical variations in the environment and transferring information to neighbouring cilia, thus propagating the chemical information in waves and creating a global response within the material. Furthermore, the self-oscillating gels were fabricated into cilia (Fig. 2b) using an X-ray lithography and micromolding technique [36,48,49]. Propagation of the chemical wave, caused by swelling/collapsing and oxidation/reduction of the gel, was observed at a velocity of 1700 µm/min with a distance between two waves of 5 mm.

The group of Prof Anna Balazs, University of Pittsburgh, was able to simulate the chemical propagation in systems based on the BZ oscillating gel [50]. They discovered that a group of cilia can 'chemically' communicate or sense the chemical environment to promote the distribution of a mechanical response. This communication depends on the distance between two cilia. Thus, closely situated cilia will bend away from each other and the chemical waves propagate 'top-down' as would be expected. However, when the distance between two cilia is increased, they will bend towards the higher concentration of the reaction activator, i.e. towards each other [51,52]. This sort of chemical response, chemotaxis, is associated with bacteria and blood cells, and the study of artificial gels can be a first step towards artificial chemotaxis.

Compared to non-polymeric small molecule oscillatory systems, polymeric materials have a number of distinct advantages, the first being the increased stability of the constructs, owing to the polymeric core. Increased stability means that oscillations are also sustained and can be continued over long periods of time with the same amplitude and duration. Secondly, such systems are recyclable and can be easily removed from the reaction medium in their collapsed state and reused in subsequent reactions. The large diversity of possible macromolecular designs (vesicles, brushes, polymersomes – only limited by the scientists' imagination) ensures that it is possible to cater for any possible function. Most importantly, the variety of compositions provides numerous opportunities for designing highly biocompatible, biodegradable materials, where the toxic heavy metal catalyst has low leaking rates and will not be released into the reaction medium. It is especially important for materials with the prospect of being used in drug delivery or wound healing. Furthermore, the BZ reaction operates in water at 37 °C, making it attractive for sustainable 'green' synthesis.

A different approach to polymeric oscillators was taken by our group led by Dr. Katarina Novakovic at Newcastle University. Rather than exploiting a polymeric catalyst, we have developed a polymeric substrate to be used in the palladium-catalysed oscillatory carbonylation reaction. This reaction, initially described by Temkin et al., exhibits redox potential and pH oscillations in a relatively simple conversion of an alkyne (in the original case – phenylacetylene; palladium-catalysed phenylacetylene oxidative carbonylation (PCPOC)) into a number of products and by-products (phenyl maleate, phenyl fumarate, and dimethoxylactone) under constant supply of carbon monoxide (CO) gas [33,53]. Catalysed by PdI_2/KI, the reaction has been the focus of our study for several years. We demonstrated oscillations within a range of temperatures (0–40 °C) that can last more than a month sustaining amplitude and range (however, due to software and equipment restrictions we were unable to track oscillations past four weeks). Furthermore, recorded pH oscillations (Fig. 3a) were synchronised with reaction exothermicity, with a 'staircase' of exothermic pulses of up to 600 J per oscillation corresponding to the drops in pH (Fig. 3b and c) [54]. The effects of the sequence of reagent addition, reaction temperature, oxidant supply, and water content on the amplitude and duration of oscillations were studied extensively in order to shed light on the mechanism of the reaction [55–57].

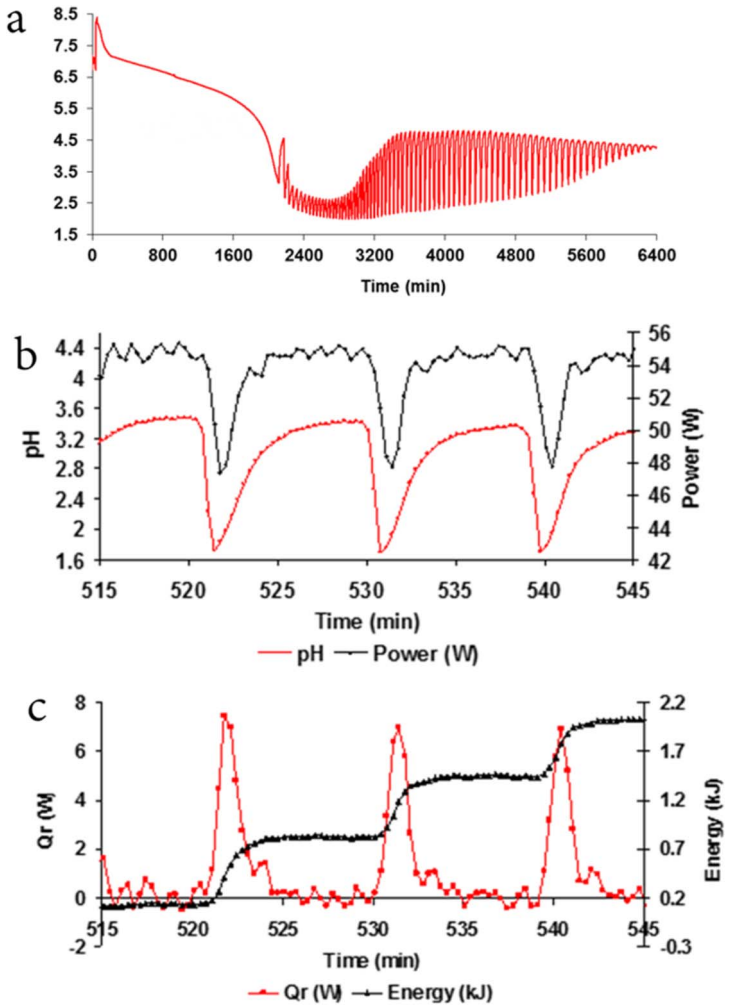

Fig. 3. (a) pH oscillations recorded in the palladium catalysed phenylacetylene oxidative carbonylation (PCPOC) reaction at 20 °C. (b) pH oscillations recorded against the exothermic power pulses. (c) 'Staircase' of exothermic pulses of energy during oscillations. Reproduced in part with permission of the PCCP Owner Societies from Ref. [55] and with permission from Elsevier from Ref. [54].

The PCPOC reaction has a number of outstanding properties. Firstly, it can proceed in both oscillatory and non-oscillatory modes with significant differences in conversion and product selectivity [58,59]. Several independent studies reported different product ratios, based on the conditions employed in the reaction – understanding the autocatalytic origins of PCPOC led to the diversity of additional reagents in the reaction mixture, including water, sodium acetate, thiourea, quinones or copper [60]. The mechanism of the reaction and which species are responsible for the oscillatory behavior continue to be topics of discussion within the community (Fig. 4). The crucial role of palladium in the reaction is indisputable, however, the oxidation state responsible for periodic oxidation and recovery is unclear and speculated [33,53,57,60,61].

An important property of PCPOC is the product selectivity in oscillatory and non-oscillatory modes, with product ratio being distinctly different for different modes, which are determined by catalyst concentration [58]. Recently we pointed out that the temperature of the reaction, besides having a direct effect on the amplitude and duration of oscillations, also dramatically changes the product selectivity [62,63]. Generally, the system is capable of generating two types of products: thermodynamic and kinetic, and at higher temperature the thermodynamic product prevails [62]. This property of the reaction is attractive for large-scale industrial applications as the reaction selectivity makes it easily tunable for generation of the desired product having the potential to decrease the costs of separation and purification. Generally, the versatility of small molecule substrates, and the reaction flexibility and tunability makes it potentially very interesting for large-scale implementation [64].

A turning point of the PCPOC reaction was recently marked by the introduction of a polymeric substrate. Our research group has, for the first time, reported reproducible oscillatory behavior in pH, using monoalkyne-terminated poly(ethylene glycol) (PEGA, Fig.5a) in place of phenylacetylene [65]. In addition to pH oscillations, synchronised oscillations in turbidity were also recorded in PEGA substrates of two molecular weights, 2000 g/mol and 5000 g/mol, demonstrating the flexibility of the system. The oscillations in turbidity indicate that non-soluble metallic palladium is released and later consumed during the oscillations suggesting that the

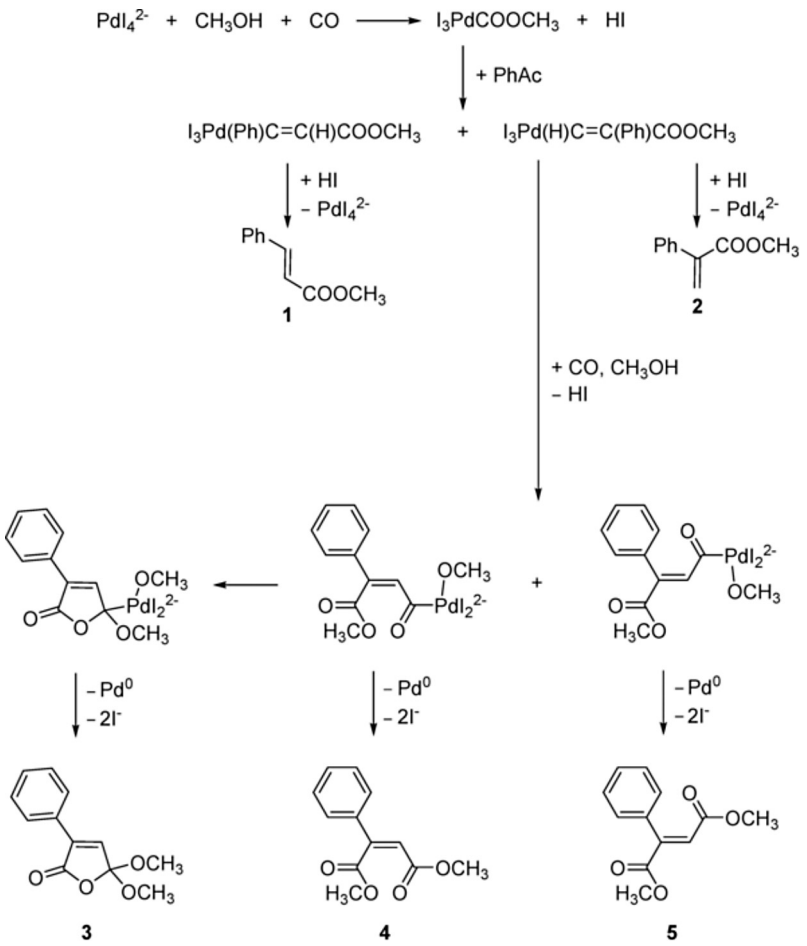

Fig. 4. Tentative mechanism for palladium iodide-catalysed oxidative carbonylation of phenylacetylene with a range of possible products, the ratio of which depends strongly on the reaction conditions. Reproduced with permission from John Wiley and Sons from Ref. [62].

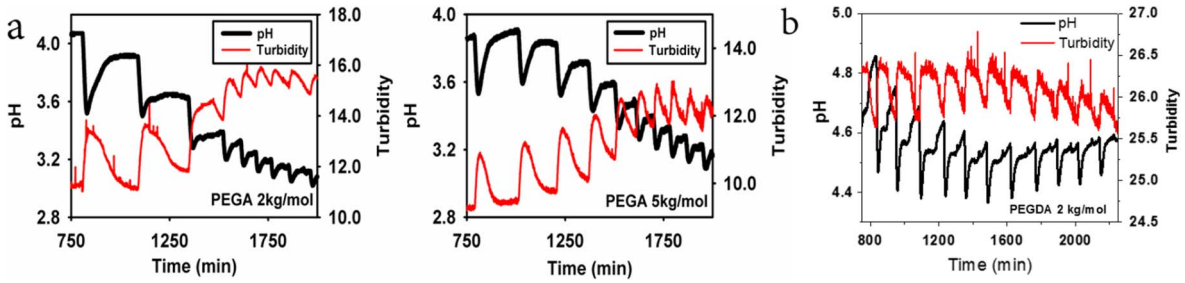

Fig. 5. Examples of oscillatory behavior experimentally recorded with (a) PEGA of 2000 and 5000 g/mol and (b) PEGDA in methanol. Reproduced with modification from [65]. PEGDA – unpublished.

mechanism given in Fig. 4 (oscillatory phenylacetylene carbonylation) likely applies to PEGA substrates. Importantly, oscillations employing PEGA are achieved using one hundred times less substrate and catalyst when compared to the reported phenylacetylene oscillatory reaction [65,66]. This drastic decrease in the concentrations of chemicals is particularly relevant to the anticipated applications. Continuing the work on polymeric substrates, we have also observed that double functionalised PEGA (PEGDA) demonstrated behavior of a similar, yet somewhat different oscillatory dynamic (Fig. 5b), the mechanisms of which still have to be studied. PEGDA is the first step towards polyfunctional substrates, and understanding the nature of oscillatory behavior in PEGDA is crucial for a smooth transition to all-polymer systems.

3. Towards an all-polymeric system for optimal drug delivery

Despite the obvious differences in Yoshida's and Novakovic's approaches and systems, their combined research outputs indicate the feasibility of the development of an 'all-polymeric' system that would combine oscillatory behavior with an auto-response, all within the same single macromolecule. Indeed, like a machine that does not drive without an engine and wheels, an ideal self-oscillatory system would incorporate all components within itself: catalyst, substrate and pH responsive gel. The architectural manipulations of the material will ensure it is suitable for the designated application.

Our major focus is smart drug delivery, one of the holy grails of current biomedical research. The key to optimal drug delivery is delivering only the amount of drug needed, when it is needed, and where it is needed. Current methods do not come close to achieving this. At present, patients often receive more medication than they need because of the inability to refine the exact dose and optimise dose timing. This excess is dangerous in terms of drug toxicity and side effects (a recognised cause of death, disability and illness) and wasteful in terms of the economic and societal costs. Optimal drug dosing is particularly challenging for diseases requiring chronopharmacotherapy where the most efficient drug delivery correlates with circadian rhythm [67]. The concept of chronopharmacotherapy seeks to maximise the therapeutic effectiveness of medication and minimise the side effects by administering a dose reflecting the daily rhythms of biofunctions. For example, peptic ulcers, in which acid secretion is high in the afternoon and at night (affects 1 in 10 people in the UK at some point); cardiovascular diseases where blood pressure is at its lowest during the sleep cycle and rises steeply during the early morning; many tumour cells differ from normal cells in their chronobiological cycle [68]. While it is widely acknowledged that appropriate timing of drug delivery enhances therapeutic outcome and minimises side effects [69], it remains difficult to achieve in practice, particularly when the ideal dosing time is during sleep and is required repeatedly. A recognised solution, ideal for illnesses that require hands-free drug delivery with a set period (i.e. pulsatile drug delivery, PDD), is the development of adequate rhythmic biomaterials capable of carrying and autonomously delivering their drug load with a specified rhythm [70,71]. Furthermore, rhythmic biomaterials are also required for advancing the areas of functional tissue engineering, regenerative medicine, development of artificial muscles and biomimetic robots. Some tissues are mechanoresponsive (bone and the vascular system) but to date no biomaterial has been developed to harness this mechanism to control cell activity and facilitate the assembly of mechanically robust and biologically functional tissue (organs) [72].

Self-oscillating architectures are ideal candidates to solve the problem of PDD – the drug can be incorporated in the body of the responsive gel, which would collapse and swell periodically, releasing the drug in pulses, following the oscillations produced by the oscillatory system bound to the gel (Fig. 6a and b) [73,74]. The beauty of such a system is that the gel can be designed to respond to a wide range of stimuli, depending on the situation: from heat (i.e. thermoresponsive gel) and pH to changes in the redox potential [75–79]. For example, the BZ reaction has found application based on its complementarity to pH-responsive pNIPAAm, and as demonstrated by Yoshida et al., this allowed the production of self-oscillating vesicles and micelles which change their size based on the oxidation state of the polymeric catalyst block [47].

A range of pH responsive gels to be coupled to oscillatory carbonylation reactions are currently under development in our laboratory. One example is a biocompatible and biodegradable genipin-crosslinked chitosan-poly(vinylpyrrolidone) gel that combines the antimicrobial and mucoadhesive properties of chitosan with the haemocompatibility of poly(vinylpyrrolidone) (PVP) and genipin, a natural crosslinking agent which exhibits fluorescence upon crosslinking (Fig. 7a) [80–85]. However, the carbonylation reaction is not limited to only pH-responsive materials. It has demonstrated redox potential oscillations too [33], and these will be attractive to employ with redox-responsive gels, for example those developed by our colleagues in the Prof Vancso group, Twente University. Their research has yielded a range of organometallic redox-responsive materials, based on poly(ferrocenylsilanes) (PFS) [86,87]. These materials could be reversibly oxidised and reduced chemically and electrochemically, demonstrating a rapid colour change and swelling/deswelling (Fig. 7b,c). Importantly, combining PFS with pH-responsive pNIPAAm, Sui et al. fabricated a dual-responsive hydrogel, sensing both the redox potential changes and the pH changes in the solution [88]. Remarkably, the gel was implemented for *in situ* synthesis of gold, silver and palladium nanoparticles due to its redox sensing properties [89–91]. The property of such gels to mediate synthesis of active nanoparticles in response to stimuli is a remarkable advantage for pulsatile drug delivery (for example, silver nanoparticles generated *in situ* exhibited antimicrobial activity) [90]. To this end, these materials have not yet been tested within an oscillatory system, and a desire to combine our scientific expertise to make the ultimate 'self-driving machines'

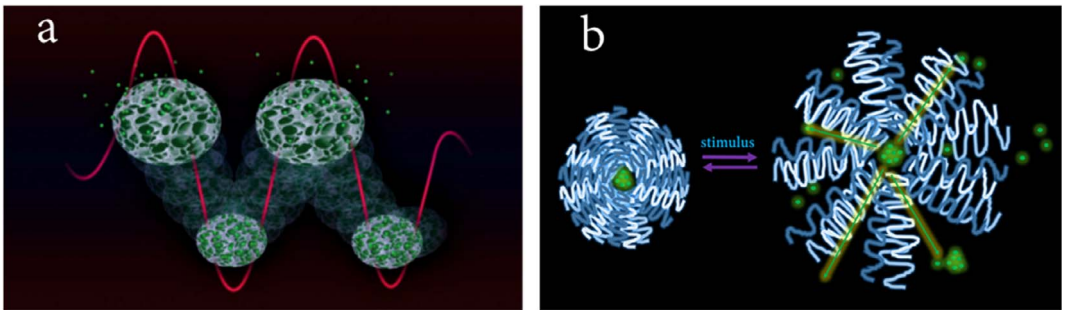

Fig. 6. Schematic illustration of (a) porous hydrogel oscillating (swelling/collapsing in volume) and simultaneously releasing payload (green) and (b) the polymersome made of oscillating hydrogel releasing molecules of drug (green) upon swelling. (a) Reproduced from Ref. [65].

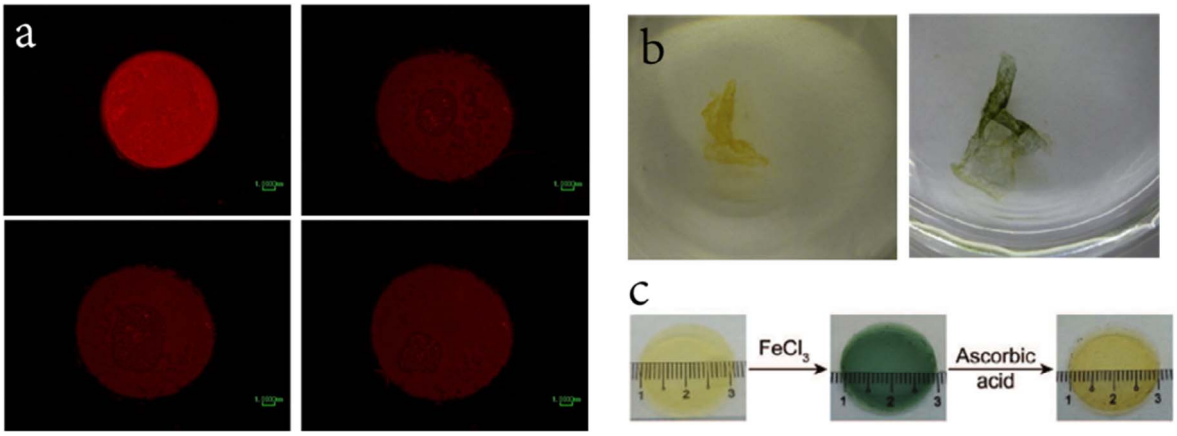

Fig. 7. (a) Crosslinking of chitosan by genipin observed by development of fluorescence. Reproduced from Ref. [92]. (b) Free-standing poly(ferrocenylsilane) PFS-PMDETA hydrogel thin film in (left) neutral and (right) oxidised state. The free-standing hydrogel thin film was oxidised with 0.1 mM $FeCl_3$. Reproduced with permission of Elsevier from Ref. [87]. (c) Reversible chemical oxidation and reduction of the pNIPAAm/PFS-VIm hydrogel. Reproduced with permission of John Wiley and Sons from Ref. [91].

is underlying our current collaborations.

A number of other research groups have been working on coupling autocatalytic reactions to polymeric materials. Prof Tony Ryan's group, University of Sheffield, designed block-copolymer physical gels and used a Landolt oscillator (reaction of iodate with ferrocyanide) to trigger mechanical actuation [34,35,93]. De Kepper and Horváth demonstrated a synergistic concept applicable to 'smart' materials, where a clock reaction was employed as a switch for the pH-responsive gel (as a positive feedback) and the gel itself served as a counter switch to bring the reaction back to the new cycle (negative feedback) [94–97].

4. The future of self-oscillating gels

The nature of oscillatory reactions still remains the key barrier to development of an 'all-polymer' PDD system. In the case of the BZ reaction, it is the substrate and the highly acidic medium that are bioincompatible, with the rates of metal catalyst leakage still unknown. Furthermore, the products of the reaction are also toxic and have to be scavenged as soon as they are generated, or alternatively substrates which form less toxic, or even naturally occurring products should be used. In addition, as the BZ reaction is short lived in a batch setup, continuous flow is required for sustained oscillations [98]. Oscillatory carbonylation reactions, on the other hand, have been discovered relatively recently and still leave much to be optimised, even though we have advanced as far as employing a polymeric substrate. To make it useful for PDD several issues need to be addressed. Firstly, the reaction is performed in methanol in laboratory conditions and as methanol is not suitable for biological applications in high quantities, alternative solvents should be researched. Parker has shown that oscillations in PCPOC system can be achieved in methanol/water mixtures suggesting that conditions better suited for biological applications are feasible. [66] Besides being a reaction medium, methanol serves as a reactant. Conveniently methanol is naturally present in the body fluids of healthy people, mainly occurring due to diet and natural microflora [99,100]. Endogenous methanol content will be sufficient for the oscillatory carbonylation reaction. A similar observation is applicable to carbon monoxide, required for the carbonylation itself. Endogenous carbon monoxide is naturally produced in the body in quantities approx. 20 μmol/h, or about 500 μM (12 ml) per day [101] and performs a number of important functions. For example, as a neurotransmitter (brain signalling molecule) and platelet aggregation inhibitor [102–105]. Therefore, in the sites of overproduction of carbon monoxide as a result of pathophysiological processes, the carbonylation reaction would additionally serve to consume the carbon monoxide and convert it to carbon dioxide. While this is more than oscillatory carbonylation reaction requires, if at specific site the endogenous carbon monoxide levels are not sufficient, there are certain approaches to obtain carbonyl functionality for the reaction. These include using: (a) metal carbonyls, such as $Co_2(CO)_8$ or $Mo(CO)_6$; (b) aldehydes or (c) carbamoylsilanes in the so called 'carbamoyl-transfer' process. All of the aforementioned types of carbonylation reagents are potentially feasible within the oscillatory system as they employ a palladium catalyst with high efficiencies [106].

Furthermore, while the organic products generated during the reaction of phenylacetylene carbonylation are not desirable, this problem was successfully eliminated by employing a polymeric substrate instead of phenylacetylene where all major products essentially remain bound to the polymer. For the all-polymeric system, a polymeric catalyst should also be introduced to complement the polymeric substrate. To this end, a complete understanding of the catalytic processes during the oscillatory carbonylation reaction is lacking, especially concerning the role of palladium and palladium-organic intermediates generated in the process. While the studies have been solidly focused on the PdI_2/KI catalytic system other oxidative catalytic systems should be now introduced. On a brighter note, major developments in polymer-bound palladium catalysts for carbonylation reactions allow the choice of the right system from a number of reported catalysts to achieve tuned oscillations [107–109].

The route to fully functional all-polymeric rhythmic systems is set and the current research directions are clear. Combined efforts in synthesis, characterisation, modelling, simulations, and deposition will in due course lead to fabrication of an all-polymer

autonomous system of low toxicity and high biocompatibility, which is the ultimate goal of our research.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eurpolymj.2017.08.033.

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